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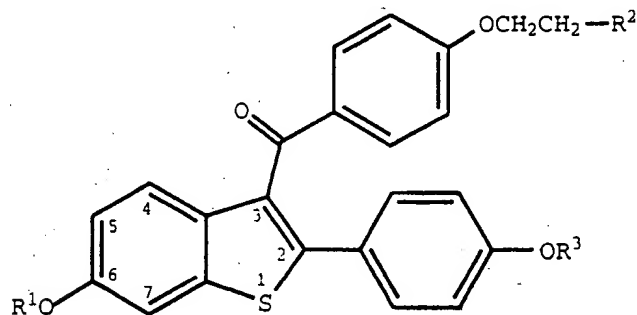
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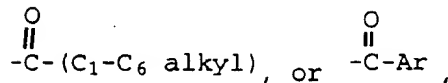
(54) Treatment of atrophy of the skin and vagina.

(57) A method of inhibiting atrophy of the skin or vagina comprising administering to a human in need thereof an effective amount of a compound having the formula



(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidine, hexamethylenamino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.

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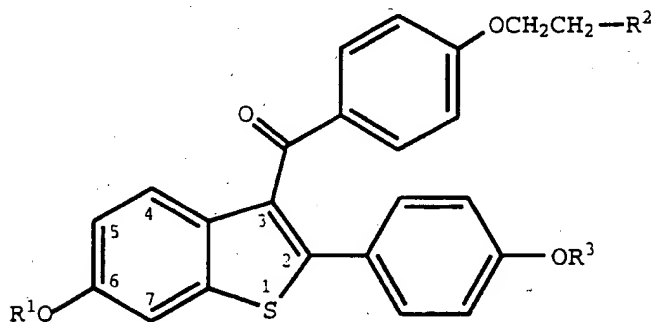
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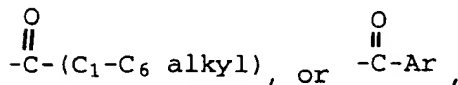
(54) **Treatment of atrophy of the skin and vagina.**

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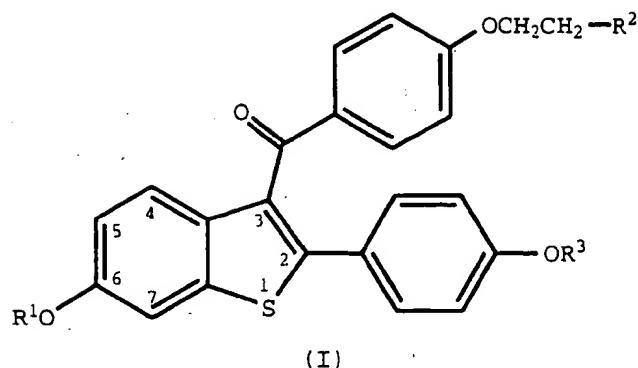
Changes in the appearance and texture of the skin with increasing age has been proverbial and well documented both quantitatively and qualitatively. It is a subject which is highly subjective in its evaluation and its ultimate effect on the individual. By in large the effect of the general atrophy of skin with age is cosmetic, but can have pathological consequences many of which are psychological in nature, i.e., the feeling of getting "old," depression, loss of sexual attractiveness, etc. In some cases, the atrophy of the skin in older people can have direct pathologies associated with it, e.g., the ability of the skin to repair in wound healing. In general, the atrophy of the skin is considered a normal and progressive consequence of the aging process and taken with "good grace." Despite the normal acceptance of aging, there is a particular time in a woman's life, i.e., the menopause, when the progressive aging pattern is greatly accelerated, especially with regard to atrophy of the vagina and skin. It is often this rapid acceleration and suddenness of change which can be contributory to pathological and psychological distress. Additionally, vaginal atrophy can lead to discomfort, e.g., itching, dryness, and painful intercourse, which can lead to a loss of sexual enjoyment and conjugal harmony and in some cases be causal in social sequelae such as divorce.

As mentioned before, the atrophy or aging of the skin can have both qualitative and quantitative aspects. The qualitative aspects are: the change of smoothness and texture, thus causing a "roughness" in look and feel on the outer surface of the skin, the change of elasticity of the skin, thus effecting the mechanical properties of the skin, and the changes in skin pigmentation. These qualitative changes result in the commonly described condition of atrophied skin as: wrinkled, rough, withered, and spotty. Quantitatively, skin aging in post-menopausal women can be measured as: a decrease in the mitotic rate of keratinocytes, changes in dermal thickness, decrease in glycosaminoglycans and soluble collagen which are linked to the moisture content of the skin, and the decrease in the urinary excretion of hydroxyproline, a measure of decrease collagen turnover. The qualitative changes in the skin, i.e., sightlessness and mechanical properties, are the result of the quantitative changes, i.e., loss or change of the extra-cellular matrix components. Therefore, it is possible to evaluate a beneficial effect of a therapy for post-menopausal skin atrophy without totally relying on subjective analysis, even though a subjective improvement may be the ultimate desired effect. In the case of vaginal atrophy, the quantitative aspect is the amount of vaginal moisture which is controlled by the amount of secretion from glands in the dermis, the qualitative result is subjective comfort.

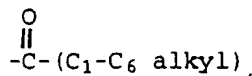
Currently, there are two major therapies available for the treatment of skin and vaginal atrophy in post-menopausal women. The first therapy is strictly a cosmetic approach, e.g., the use of make-up, skin moisturizers, night cremes, vaginal lubricants, etc. Although this cosmetic therapy does not affect the underlying physiological cause of the atrophy, often it does achieve some subjective benefit for the individual. The second type of therapy involves the treatment of the underlying physiological causes with active, medicinal agents, most notably Vitamin A and estrogens. Vitamin A is used, its effectiveness is controversial, and it is known to have substantial, undesirable side-effects which limit its use.

At the time of menopause, the levels of estrogen produced by the ovaries rapidly decrease. This decrease in estrogen has pronounced effects on the skin and vagina causing a rapid acceleration in the natural process of atrophy. Estrogen replacement therapy is often beneficial in treating skin and vaginal atrophy. However, estrogen replacement therapy has undesired side-effects, most serious of which is the potential for the development of the threat of cancer. The inclusion of progestinal agents leads to undesirable psychological effects. The use of estrogen replacement therapy for the sole purpose of treating skin and vaginal atrophy is not common because of the negative side-effects. Clearly, an effective and safe agent which positively effects the underlying physiology and thus improves the qualitative aspects of skin and vaginal properties in post-menopausal women would be useful.

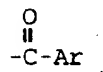
This invention provides methods for inhibiting atrophy of the skin or vagina comprising administering to a human in need thereof an effective amount of a compound of formula I



wherein R¹ and R³ are independently hydrogen, -CH₃,



or



wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-arylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting the atrophy of the skin or vagina. The methods of use provided by this invention are practiced by administering to a human in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit the atrophy of skin or vagina. The term inhibit is defined to include its generally accepted meaning which includes prophylactically administering to a human subject to incurring the conditions described, and holding in check and/or treating existing conditions. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

Raloxifene, a preferred compound of this invention is the hydrochloride salt of a compound of formula 1, wherein R¹ and R³ are hydrogen and R² is 1-piperidiny!, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

Raloxifene and selected analogs are safe and effective agents which have a positive effect on the underlying, physiological mechanisms seen in skin and vaginal atrophy. The result of this positive effect by raloxifene and selected analogs is the improvement of the qualitative properties of the skin and vagina.

Generally, a compound of formula 1 may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, administered

by the intramuscular or intravenous routes, or administered topically. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Optionally substituted phenyl includes phenyl and phenyl substituted once or twice with C₁-C₆ alkyl, C₁-C₄ alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I via non-topical administration required to inhibit skin or vaginal atrophy according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day,

or more often as needed.

For topical administration, the compounds may be formulated as is known in the art for direct application to an area. Conventional forms for this purpose include ointments, lotions, pastes, jellies, sprays, and aerosols. The percent by weight of a compound of the invention present in a topical formulation will depend on various factors, but generally will be from 0.5% to 95% of the total weight of the formulation, and typically 1-25% by weight.

The compositions can take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension.

These compositions can contain pharmaceutically acceptable vehicles and adjuvants which are well known in the prior art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, ethanol, isopropyl alcohol, glycol ethers such as the products sold under the name "Dowanol", polyglycols and polyethylene glycols, C₁-C₄ alkyl esters of short-chain acids, preferably ethyl or isopropyl lactate, fatty acid triglycerides such as the products marketed under the name "Miglyol", isopropyl myristate, animal, mineral and vegetable oils and polysiloxanes.

The compositions according to the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They can also contain gums such as xanthan, guar or carob gum or gum arabic, or alternatively polyethylene glycols, bentones and montmorillonites, and the like.

It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes and colourings. Also, other active ingredients may be added, whether for the conditions described or some other condition.

For example, among antioxidants, t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and α -tocopherol and its derivatives may be mentioned.

The galenical forms chiefly conditioned for topical application take the form of creams, milks, gels, dispersions or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, or alternatively the form of aerosol formulations in spray or foam form or alternatively in the form of a cake of soap.

Formulations

In the formulations which follow, "active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of raloxifene that may be made include those shown below:

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.
A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

	Ingredient	Quantity (mg/tablet)
5	Active ingredient	0.1 - 1000
	Cellulose, microcrystalline	0 - 650
	Silicon dioxide, fumed	0 - 650
10	Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

	Ingredient	Quantity (mg/tablet)
20	Active ingredient	0.1 - 1000
	Starch	45
	Cellulose, microcrystalline	35
25	Polyvinylpyrrolidone (as 10% solution in water)	4
	Sodium carboxymethyl cellulose	4.5
	Magnesium stearate	0.5
30	Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

Formulation 8: Suspensions

	Ingredient	Quantity (mg/5 ml)
45	Active ingredient	0.1 - 1000 mg
	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 mg
	Benzoic acid solution	0.10 mL
50	Flavor	q.v.
	Color	q.v.
	Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

The following topical compositions are prepared:

Formulation 9

5

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

10

Formulation 10

15

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Ethyl lactate	15.0 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

20

25

Formulation 11

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.0 g
Butylated hydroxytoluene	0.02 g
Active Ingredient	1.5-25 g
Ethanol qs	100 g

30

35

Formulation 12

40

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Butylated hydroxytoluene	0.01 g
C ₈ -C ₁₂ fatty acid triglycerides	10.0 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

45

50

55

Formulation 13

Ingredient	Quantity (mg/5 ml)
Isopropanol	46.0 g
Active Ingredient	1.0-15 g
C ₈ -C ₁₂ fatty acid triglycerides	49.0 g

Formulation 14

Ingredient	Quantity (mg/5 ml)
Ethanol	69.0 g
Ethyl lactate	10.0 g
Active Ingredient	1.5-20 g
C ₈ -C ₁₂ fatty acid triglycerides	30.0 g

Formulation 15

Ingredient	Quantity (mg/5 ml)
Isopropanol	47.0 g
Acetone	10.0 g
Ethyl lactate	10.0 g
Active Ingredient	1-15 g
C ₈ -C ₁₂ fatty acid triglycerides	30.0 g

Formulation 16

Ingredient	Quantity (mg/5 ml)
Ethanol	95.08 g
Butylated hydroxytoluene	0.02 g
Active Ingredient	1.5-25 g

Formulations 13, 14, 15, and 16 take the form of lotions.

Formulation 17

Ingredient	Quantity (mg/5 ml)
White vaseline	50.0 g
Liquid paraffin	15.0 g
Refined paraffin wax	32.0 g
Active Ingredient	1-20 g

Formulation 18

Ingredient	Quantity (mg/5 ml)
White vaseline	50.0 g
Liquid paraffin	13.0 g
Refined paraffin wax	32.0 g
Active Ingredient	1-20 g

Formulations 17 and 18 take the form of sticks.

AssaysSkin Atrophy

Three to twenty women, who are post-menopausal and in good health, are selected. Additionally, these women are selected on the basis of their presenting several signs of rapid dermal atrophy, such as a rapid increase in the number of facial wrinkles or crow's feet, rapid change in the pigmentation of the skin, i.e. "age spots", or other complaints of rapid dermal aging. It should be remembered by the attending physician that these criterion may be highly subjective to the patient and that some consideration must be taken into account in patient selection. Also, dermal atrophy may be the result of other factors such as UV damage from the sun or other environmental insults and that such patients who are suffering from these effects would be excluded.

The first component of the study is qualitative and subjective one, i.e., an evaluation of improvement in the patient's appearance. Such an evaluation requires an initial benchmark for future comparison. Some initial benchmarks might be in the form of a standardized set of questions as to how the patient views her own appearance, photographs of the patient, or a psychological profile of the patient's self-image. The second component is quantitative; these include the measurement of urinary excretion of hydroxyproline, moisture content of the skin, glycosaminoglycans in the skin, and changes in resilience and pliability of the skin. Methods for determining these factors are found in "The Menopause", Ed. R.J. Beard, University Press, Chapter 7 (1977) and "Methods in Skin Research", Ed. Skerrow, D. and Skerrow C. J., John Wiley & Sons Ltd., Chp. 22, "Analysis of Sebaceous Lipids", p. 587-608 (1985), and further references cited therein, all herein incorporated by reference. Again, an initial benchmark of these quantitative factors is obtained.

The women, thus selected and initially evaluated, are placed in a clinical protocol of receiving 40-400 mg of an active compound of this invention by oral administration either as a single or split dose. Alternatively, these patients are placed in a protocol for topical administration to areas of the skin most effected by the atrophy. This topical protocol includes the use of a suitable formulation containing 5-50% (by weight) of an active compound of this invention applied to the affected area once or twice a day. Either of these protocols continues two to twelve months. Subsequent evaluations, both quantitative and qualitative, are made at appropriate intervals.

A positive result is an improvement in the overall qualitative index of the patient's appearance and/or an improvement in the quantitative parameters, e.g., an increase in the urinary excretion of hydroxyproline signifying an increase in turnover and synthesis of collagen, an increase in moisture content, glycosaminoglycans, pliability, or resilience of the skin.

Vaginal Atrophy

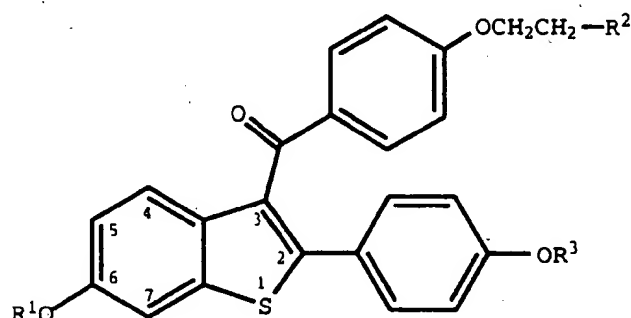
Three to twenty women suffering from vaginal atrophy associated with menopause are selected. These women are in general good health. Since the nature of this disorder is highly idiosyncratic and subjective, evaluation of the effectiveness of treatment would necessarily be subjective in nature. These patients are asked to keep a daily log noting such details as vaginal itching and scaling and the degree of comfort in sexual intercourse. These women are placed on a clinical protocol similar to that described above for atrophy of the skin. Particular emphasis is placed on the use of vaginal suppositories containing 5-25% of an active compound of this invention.

A positive result is an improvement in the comfort of sexual intercourse and/or a decrease in vaginal itching or scaling.

Utility of the compounds described herein is exhibited by the positive results observed in one or both of the above assays.

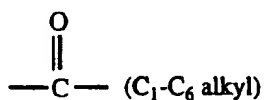
Claims

1. The use of a compound having the formula

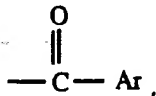


(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



or

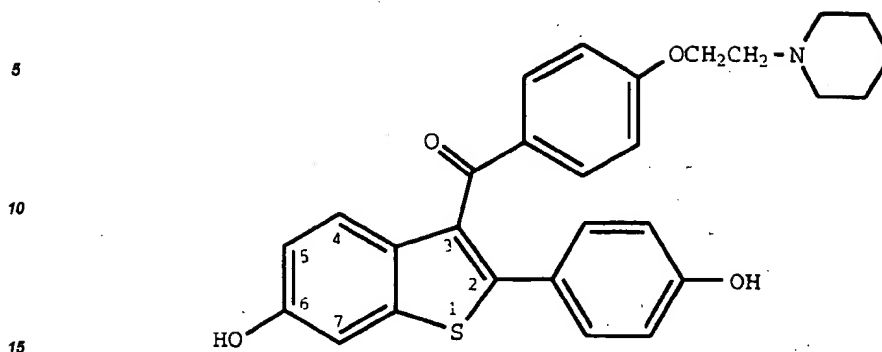


wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting skin atrophy.

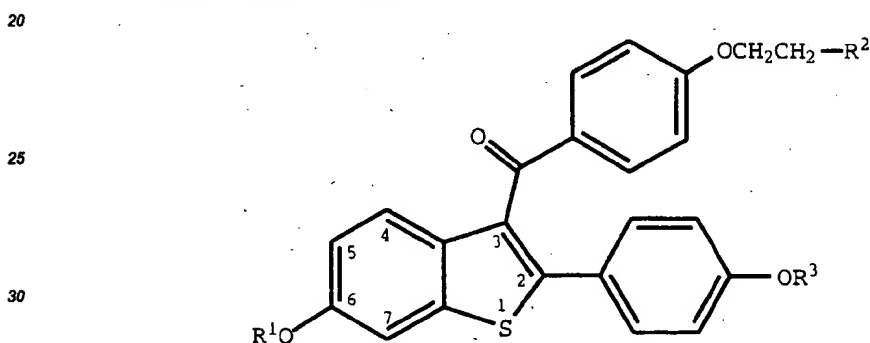
2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.
3. The use of Claim 1 wherein said medicament is prophylactic.

4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.

5. The use of a compound having the formula



(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



45 or



wherein Ar is optionally substituted phenyl;

55 R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting vaginal atrophy.

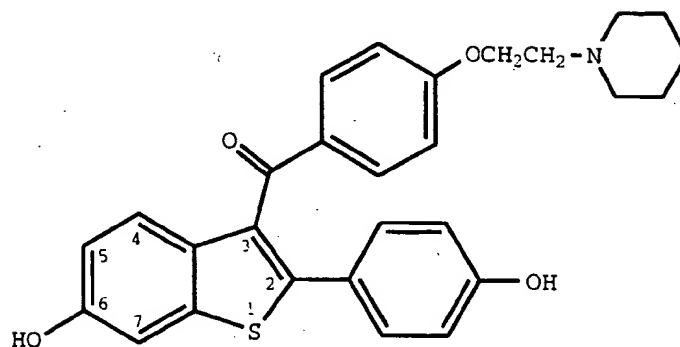
6. The use of Claim 5 wherein said compound is the hydrochloride salt thereof.

7. The use of Claim 5 wherein said medicament is prophylactic.
8. The use of Claim 5 wherein said compound is

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or its hydrochloride salt.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 9467

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
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Place of search MUNICH		Date of completion of the search 5 April 1995	Examiner Foerster, W
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>A : member of the same patent family, corresponding document</p>			

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